UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/661,658 | 09/14/2000 | Andrew D. Ellington | 119927-1021 | 9207 |

30623 7590 12/16/2005

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

| EXAMINER | |
|---|---|
| GIBBS, TERRA C | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 12/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/661,658 | ELLINGTON ET AL. | |
| | Examiner | Art Unit | |
| | Terra C. Gibbs | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7,12-19,21 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *7* is/are allowed.

6)☒ Claim(s) *1-5, 12-19, ans 26-28* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed September 9, 2005.

Claims 7 and 21 have been amended. Claims 1-5, 7, 12-19, 21, and 26-28 are pending in the instant application.

Claims 1-5, 7, 12-19, 21, and 26-28 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Specification*

In the previous Office Action mailed March 9, 2005, the disclosure was objected to because the amendment to the specification filed December 30, 2003 recited, "Fig. 3a" where only "Figure 3" can be found. **This objection is withdrawn** in view of Applicant's amendment to the specification to recite "Figure 3".

### *Claim Rejections - 35 USC § 103*

In the previous Office Action mailed March 9, 2005, claims 1-5, 12-19, and 26-28 were rejected under 35 U.S.C. 103(a) as being unpatentable over Soukup et al. (Proc. Natl. Acad. Sci, 1999 Vol. 96:3584-3589, Applicant's reference [C51], filed September 30, 2003) or Robertson et al. (Nucleic Acids Research, 2000 Vol. 28:1751-1759,

Applicant's reference [C44], filed September 30, 2003). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed March 9, 2005.

***Response to Arguments***

In response to this rejection, Applicants traverse the Examiner's characterization that the hammerhead ribozyme, the ligase ribozyme, and the Group I intron ribozyme are functionally equivalent. Applicants argue that the Examiner has concluded that "all ribozymes function similarly" and are therefore "art-recognized functional equivalents" without presenting or citing any documentary evidence to support this assertion. Applicant's also argue that the Examiner has failed to establish a *prima facie* case of obviousness with regard to the Soukup and/or Robertson references since there is no teaching or suggestion in either the Soukup or Robertson reference that the hammerhead ribozyme or the ligase ribozyme, when coupled to an aptamer oligonucleotide, will have the same functionality as an aptazyme that contains a Group I intron oligonucleotide. Applicants contend that the Robertson reference teaches away from the ribozymes being functionally equivalent since this reference specifically chose to use the smaller ligase ribozyme to study allosteric regulation rather than a larger ribozyme, such as the Group I intron ribozyme. Applicant's argue that there is no teaching or suggestion in the Soukup or Robertson references that a Group I intron ribozyme of the claimed invention will experience the same level of allosteric regulation, as a smaller, less structurally stable ribozyme, e.g. the hammerhead or ligase

ribozymes. Applicants conclude that the teachings of the Soukup or Robertson references fail to provide a skilled artisan with a reasonable expectation that a Group I intron can be successfully subjected to allosteric regulation when coupled to an aptamer sequence.

Applicant's arguments have been fully considered but are not found persuasive. Applicant is of the opinion that hammerhead ribozymes, ligase ribozymes, and Group I intron are not functionally equivalent. In the previous Office Action mailed March 9, 2005, the Examiner detailed her reason's why one skilled in the art would readily accept that hammerhead ribozymes, ligase ribozymes, and Group I intron ribozymes are equivalents since these three ribozymes function in a similar manner. For example, the previous Office Action at page 6 recites, "One of ordinary skill in the art would readily accept that ribozymes, in general, are RNA that can act as enzymes by catalyzing the cleavage or ligation of other target RNA molecules. Generally, engineered ribozymes bind target RNA in a sequence specific manner to cleave or ligate their targets."

The general fact that ribozymes functional similarly is concurred in the instant specification at page 2, lines 8-11 where it states, "ribozymes or RNA enzymes are oligonucleotides of RNA that can act like enzymes by catalyzing the cleavage of RNA molecules. Generally, ribozymes have the ability to behave like an endoribonucleases". The instant specification goes on to teach, "regulatable ribozymes have been described, wherein the activity of the ribozyme is regulated by a ligand binding moiety" (see page 3, first few lines). The instant specification also teaches, "the regulatable ribozymes described to date target, bind, e.g. a first target sequence and the enzymatic activity is

brought to bear on a separate RNA molecule for cleavage" (see page 3, last few lines). Given this general disclosure, the Group I intron ribozyme, like the hammerhead and ligase ribozymes, acts like an enzyme by catalyzing the cleavage of RNA molecules. Similarly, the Group I intron, like the hammerhead and ligase ribozymes, has the ability to behave like an endoribonuclease. As the instant specification teaches, the regulatable ribozymes described to date targets and binds a target sequence. It is noted that the Group I intron also targets and binds a target sequence in the same general manner as those ribozymes described to date in the prior art. Simply put, since the Group I intron oligonucleotide, the hammerhead ribozyme, and the ligase ribozyme all behave in a similar manner to catalyze the cleavage of RNA molecules, they are considered to be art-recognized functional equivalents.

Regarding Applicant's argument that there is no teaching that suggests the Group I intron will exhibit allosteric control like the hammerhead ribozyme and the ligase ribozyme, this is not found persuasive because as argued above, since the Group I intron oligonucleotide, the hammerhead ribozyme, and the ligase ribozyme all function in a similar manner, they are considered to be art-recognized functional equivalents. Given that the Group I intron, the hammerhead ribozyme, and the ligase ribozyme are functional equivalents, there is no reason to believe that they will not function similarly, e.g. exhibit some degree of allosteric control, when coupled to an aptamer oligonucleotide.

Regarding Applicant's argument that the Robertson reference teaches away from the Group I intron and ligase ribozymes as being functionally equivalents, this is not

found persuasive. The Robertson reference teaches, "[T]he chief advantage of the L1 ligase is its small size, 130 nt, since we suspected that ligand-induced conformational changes would have a proportionately larger influence on a small, relatively unstable ligase as opposed to a larger, more structurally robust ligase (such as the Group I intron)" (see page 1751, second column, first paragraph). This statement is a mere opinion of why the Robertson Group chose a ligase ribozyme over a Group I intron oligonucleotide. In fact, the Robertson reference explicitly states, "*we suspected*" that ligand-induced conformational changes would have a proportionately larger influence on a small ligase as opposed to a larger ligase. This does not teach that the ligase ribozyme and the Group I intron are not functionally equivalent, but instead lends credence to the fact that the ligase ribozyme is smaller than the Group I intron, and the ligase ribozyme *may* [emphasis added] undergo a ligand-induced conformational change more readily than the Group I intron. The Examiner would like to add that the Robertson reference also teaches, "ribozyme ligases can be readily engineered to function as allosteric enzymes, and reveal that many of the techniques and principles previously demonstrated during the development of hammerhead aptazymes may be generalizable" (see Abstract). This statement actually teaches that the same rationale used to make hammerhead aptazymes can be generally used with ribozymes other than the hammerhead.

In summary, ribozymes whose activities are modulated by effector molecules have previously been engineered. Adjoining aptamers to allosteric ribozymes has also been described in the art. It is well known in the art that Group I intron oligonucleotides,

hammerhead ribozymes, and ligase ribozymes act similarly like endonucleases to catalyze the cleavage of RNA molecules. Thus, it is the Examiner's position that one of ordinary skill in the art would recognize that the hammerhead ribozyme (as taught by Soukup et al.), the ligase ribozyme (as taught by Robertson et al.), or the Group I intron ribozyme of the instant invention are functionally equivalent. The instant specification has disclosed that "regulatable ribozymes have been described, wherein the activity of the ribozyme is regulated by a ligand binding moiety". There is no functional difference between those regulatable ribozymes previously described in the art (e.g. hammerhead and/or ligase ribozymes, for example) and the Group I intron oligonucleotide of the instant invention. In this regard, the Examiner has established a *prima facie* case of obviousness in maintaining that the hammerhead ribozyme, the ligase ribozyme, and the Group I intron are functional equivalents.

Applicant's amendment necessitated the new grounds of rejection presented below:

***Claim Objections***

Claim 21 is objected to because of the following informalities: Claim 21 recites "A allosterically regulatable aptazyme" and is grammatically incorrect as the claim should read "An allosterically regulatable aptazyme". Appropriate correction is required.

### *Allowable Subject Matter*

Claim 7 is allowable. The art does not teach or fairly suggest a regulatable aptazyme comprising a Group I intron oligonucleotide and an aptamer oligonucleotide, wherein the aptazyme comprises SEQ ID NO:2.

### *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
December 1, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600